UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/630,319	07/31/2000	Arthur M. Krieg	C1039.70042US00	5464

7590 03/24/2008

Helen C Lockhart
Wolf Greenfield & Sacks P C
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
03/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/630,319	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/20/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90,93,96,98-101,104,133-142,144-146 and 149-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90,93,96,98-101,104,133-142,144-146 and 149-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/20/04, 08/27/04, 08/30/04, 10/28/04, 05/31/05+12/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/2007 has been entered.

Status of Claims

2. Claims 1-89, 91-92, 94-95, 97, 102-103, 105-132, 143 and 147-148 are cancelled. Claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 are pending and under examination.

Information Disclosure Statement

3. The information disclosure statements filed 08/20/04, 08/27/04, 08/30/04, 10/28/04, 05/31/05 and 12/20/07 have been considered and attached with this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The written description rejection is withdrawn in view of Applicant's submission.

6. Claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the rejection, Applicant argues that it is unclear why the practice of the claimed method would require undue experimentation especially it is not the unity of the claimed invention is not being challenged. Applicant submits that in order to practice the claimed invention, one of ordinary skill in the art would simply need to administer the oligonucleotides encompassed by the claimed invention

Applicant's submission has been considered, however, it is not found persuasive. It should be clear that the Office does not doubt the utility of the claimed invention. The Office would have issued a lack of utility rejection based had the Office doubted the utility of Applicant's claimed invention. It appears that Applicant has misconstrued the enablement rejection. The enablement rejection is directed at the make and use of the claimed invention. While it clear that anyone, including those outside the art, reading the claims would be able to perform the active steps recited in the claims. The active steps are directed at the administration of CpG containing oligonucleotides. However, neither the ordinary person nor those skilled in the art would know how to use the oligonucleotides to treat bacterial infections. In the instant case, it is well known in the CpG art that bacterial DNA contains these CpG motifs that are found to be

immunostimulatory. And that these immunostimulatory activities induce a Th1 biased immune response that noted to be important in resolving infections. However, neither Applicant nor the art teach of a single oligonucleotide that treats infection. Thus, in a way, it can be stated that Applicant has not taught the skilled artisan how to make an oligonucleotide that treats bacterial infection. All that Applicant and the art teach is the use of the oligonucleotides as an adjuvant to vaccines because the observed immunostimulatory activities of the oligonucleotides. As stated in the previous office action, Applicant has only provided an association study between the ability of the oligonucleotides to stimulate a Th1 biased immune response and the importance of the stated immune response to resolve infections. That is all that Applicant has provided. Applicant has not provided any additional teachings or guidance that would enable the skilled artisan to harness the activities of the CpG oligonucleotides to render it therapeutic in the manner required by the claimed invention. Thus, while Applicant may have asserted that the Office questioned the credible utility of the claimed invention, such is not the case. The Office finds that the claimed invention is not enabling the skilled artisan how to make and use it without undue experimentation.

Applicant further submits the disclosure of Totte et al., Bohn et al., and Autenrieth et al. to demonstrate that the art recognizes the use of cytokines to treat bacterial infections. Applicant further argues that the claimed invention is not directed at the administration of exogenous cytokines, and noted that the results observed from such administration does not translate directly to results achieved with endogenous induction of cytokines.

Applicant's submission has been considered, however, it is not persuasive. The Office has reviewed each of the references cited. It should be noted that the teachings provided in the references are mainly directed at establishing a relationship between IFN-gamma and bacterial infections. The references do not establish the use of oligonucleotides, which induces the production of an array of Th1 associated cytokines, including IFN-gamma, to treat bacterial infection. As Applicant has noted in the arguments, the results observed from such administration does not translate directly to results achieved with endogenous induction of cytokines. Hence, while these references may provide a relationship between IFN-gamma and bacterial infection, they fail to establish that CpG oligonucleotides treat bacterial infection. Applicant has not even established that the oligonucleotides are capable of inducing the required level of IFN-gamma to impart any influence on bacterial infection. It should further be noted that, as stated in the previous office action, the art (Krieg et al.) advised that each oligonucleotides is distinct from one another because each induces a different immune profile, e.g. stimulation of different cytokines and at different level. Furthermore, the art has also noted an absence of in vivo and in vitro correlation among species. See Mutwiri et al. Overall, Applicant has not establish the type of immune profile necessary for treating bacterial infection and the oligonucleotides that are capable of inducing the required immune profile. All that exists is an association between the ability of CpG oligonucleotides to induce a Th1 immune response and the general significance of such response in resolving bacterial infection. It should further be noted that the Office cited the cytokine arts to establish the level of unpredictability noted with the administration of

exogenous cytokines. This lack of predictability would necessary exists whether the cytokine is endogenously induced by the administration of CpG oligonucleotides. In the regard, it should further be noted that Applicant has not even taught the skilled artisan how to "turn on" the right set of cytokines to resolve the infection encompassed by the claimed invention.

Applicant additionally revisits the teachings of Auricchio et al., Klinman, Conover and Coban, and Raghavan et al. With Auricchio et al., applicant argues that the references teaches the use CpG oligonucleotides to treat bacterial infections, and that the questions of further characterization of the mechanism of such action does not render the teachings of Auricchio et al. unpredictable. With Klinman, Conover and Coban, Applicant argues that the authors describe therapeutic regiments for treating infection, and that the development of clinical regiments for the treatment of bacterial infection is within the skill of the ordinary artisan. With Raghavan et al., Applicant corrects the Office interpretation of this reference. Applicant notes that the reference notes that CpG does not have a directed antibacterial effect rather a lack of correlation between in vivo and in vitro data.

Applicant's submission has been considered, however, it is not found persuasive. Regarding the teachings of Auricchio et al., the reference does not teach the use of CpG oligonucleotide in the treatment of bacterial infection as alleged by Applicant. The reference teaches the killing, not the treating of infection. These are distinct from one another. Additionally, the further characterization of the mechanism does not establish that Auricchio et al. is unpredictable, as asserted by Applicant; however, it does

establish that the use of CpG oligonucleotide is unpredictable for the mechanism of action is not even known. In the absence of mechanism of action, the skilled artisan would not readily be able to arrive at the claimed invention without undue experimentation. The same is noted of Raghavan et al., who establishes that the mechanism of action for CpG oligonucleotides is unknown.

Regarding Klinman, Conover and Coban, the Office cited the reference to demonstrate that therapeutic benefit also depends on a limited number of settings. The presence of only a limited number of settings evidences that the skilled artisan practicing the claimed invention will have a difficult time doing so. Compounding with this and other noted difficulties that surround the nature of the claimed invention, it would be impossible for the skilled artisan to practice the claimed invention without an undue burden of experimentation.

Applicant further criticizes the Office for noting that the claimed invention is not limited to the type of subjects being treated, especially those proficient or deficient for the IFN-gamma gene. Applicant specifically notes that it is unclear how this argument reads on enabling issue noted of record. Applicant also criticizes the Office for citing the use of different treatment regimens for different bacteria.

Applicant's criticism as been noted, however, it is not found persuasive. As stated in the previous office action Juffermans provides that protective immunity varies among IFN-gamma gene proficient and deficient mice. This finding speaks to the breadth of Applicant's claimed invention. Applicant's claimed invention is not limited to subjects that are proficient or deficient in the IFN-gamma gene. That is, it is clear that

Applicant's claimed invention is not enabling for subjects that lack the IFN-gamma gene since they lack the gene and the gene is necessary for protective immunity. This teaching obviously points out that the full scope of the claimed invention is not enabling. Thus, while IFN-gamma gene deficient subjects are not typical subjects, they remain encompassed by the claimed invention.

Additionally, as stated previously, Juffermans teaches use of different treatment regimens for different bacteria. In the instant case, Applicant's claimed invention is directed at a single treatment regiment for all bacteria. The fact that different treatment regimens are necessary for different bacteria evidences a lack of predictability. One current treatment does not treat all bacteria infections. This also demonstrates that the skilled artisan practicing the claimed invention would not only have to make oligonucleotides that treat bacteria infection the skilled artisan would also have to blindly experiment with different treatment regimen for different bacteria. This along with the many experiments that the skilled artisan would have to conduct practicing the claimed invention and the large absence of predictability in the art evidences that skilled artisan would not be able to practice the claimed invention without undue experimentation.

Applicant further notes that the specification does not teach one skilled in the art to blindly administer any CpG oligonucleotides any does to activate an unknown immune response. Applicant argues that the oligonucleotide can be administered to produce a specific immune response associated with the induction of certain kind Of cytokines, as well as b and NK cell activation, and that the identification of a dose that is useful in human subjects does not require undue experimentation.

Applicant's submission has been considered, however, it is not found persuasive. Applicant is correct to argue that the identification of a dose that is useful in human subjects does not require undue experimentation. However, this is directed at the perfecting of a therapeutically effective treatment regimen. In the instant case, Applicant has yet to perfect the claimed invention. Applicant fails to teach the skilled artisan how to harness the immunostimulatory activities of CpG oligonucleotides to render it therapeutically effective against bacteria infection. Thus, in the absence of an oligonucleotide that is therapeutically effective against bacteria infection, the skilled artisan would not readily be able to identify a dose that is useful in human subjects. The undue experimentation here is not directed at perfecting treatment regimen and protocols, it is directed at the making of oligonucleotides that treat bacteria Infections, as encompassed by the claimed invention.

Applicant also argues that the reduction in bacterial growth demonstrated by Hayashi et al is a treatment regimen for bacterial infection using CpG oligonucleotide.

This argument has been considered, however, it is not found persuasive. As expressed in the previous office action, a difference in scope exists between the claimed invention and the disclosure of Hayashi et al. A reduction in bacterial growth does not equate to the treating bacterial infection in a subject. The Office agrees that the treatment of bacterial infection does not necessarily require complete removal of the infectious organism. Similarly, it follows that a reduction in bacterial growth does not equate to the therapeutic treatment of bacterial infection in a subject.

It is further noted that Applicant has taken issue with the Office's citation of Klinman, Verthelyi, Takeshita and Ishii on the risk of using CpG or DNA vaccines to stimulate innate or adaptive immunity. To this point, Applicant argues that this issue falls within the scope of the FDA not PTO. Applicant also notes that the discovery of the CpG oligonucleotides can be promising in the treatment of infections does not support the unpredictability of the claimed invention.

This argument has been considered, however, it is not found persuasive. In the instant case, the Office recognizes it is not the FDA. However, the citation of Klinman, Verthelyi, Takeshita and Ishii is used to demonstrate the challenges that the skilled artisan would encounter practicing the claimed invention. The Office clearly is not directed at regulating DNA vaccine use, however, the Office is directed at evidencing that the skilled artisan would not be able to practice the claimed invention without undue experimentation based on the Wands factors. Applicant's assertion that the discovery of the CpG oligonucleotides can be promising in the treatment of infections does not support the unpredictability of the claimed invention has been noted. And, Applicant is correct to note that the discovery itself does not make the claimed invention unpredictable. It is the unpredictability in noted in the art, as directed at the use of CpG oligonucleotides as the active ingredient against infections that render the claimed invention not enabling.

It is noted that throughout Applicant's submission, Applicant argues that various references, including Elkins et al., teach that CpG oligonucleotides protect mice from bacterial infection. Regarding this argument, the Office reminds Applicant that the

claimed invention is not directed at protecting subjects from infections, it is directed at treating bacterial infections in subjects in need thereof.

Applicant's clarification that Elkins et al. was published subsequent to the priority date of the instant application is noted.

In addition to above, and similar to previous submission by Applicant, Applicant argues that the Office has failed to address Applicant's arguments. It is noted that Applicant argues that most of the references cited by the Office is not relevant to the claimed invention.

Applicant's criticisms have been noted, however, because Applicant has disclosed in the specification that the claimed invention relies on the immunostimulatory activities of oligonucleotides comprising CpG motifs to treat bacterial infection. Specifically, Applicant disclosure suggests taking advantage of the Th1 biased immune response induced by the oligonucleotides to treat bacterial infection. In association with a Th1 immune response is the induction of Th1 associated cytokine profiles. The induction of Th1 associated cytokines necessarily follows the production of a Th1 immune response. Hence, the Office cited the teachings of the cytokine arts. These teachings demonstrated that the direct administration of cytokines itself is unpredictable. Hence, if the direct administration of cytokines is unpredictable, it logically follows that the indirect administration of cytokines, via stimulation of a Th1 biased immune response, would necessarily be unpredictable, if not more unpredictable.

In is further noted that Applicant notes that the teachings of Infante-Duarte et al. is not inconsistent with the claimed invention. This has been considered, however, it is

not sufficient to overcome the rejection. Like the other references, Infante-Duarte et al. fails to enable the skilled artisan how to practice the claimed invention without undue experimentation. While the disclosure of Infante-Duarte may not be "inconsistent" with the claimed invention, but neither the reference nor the instant application teaches the skilled artisan how to harness the Th1 immune response or immunostimulatory activities of CpG oligonucleotides to treat, prevent or ameliorate viral infection without undue experimentation. Rather than enabling the claimed invention, Infante-Duarte et al. outlines the challenges in harnessing the immune response to resolve intracellular infections.

In addition to above, Applicant criticizes the Office's interpretation of Krieg and Mutwiri et al. Applicant argues that Office conclusion that the absence of TLR9 in some species would lead to variability in results is misplace, and notes that Mutwiri et al. discloses that in vitro stimulation of cells by CpG motifs is conserved across species. In response to the Office position that every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies…etc.," Applicant argues that Applicant has described a class of oligonucleotides comprising the CpG motif that favors a Th1 immune response, and that variability in the immune response induced by the oligonucleotides should not be the cause for a lack of enablement. Applicant further argues that the statement that the "immunostimulatory activity of CpG oligonucleotides is species specific," does not support a lack of enablement.

Applicant's position has been carefully considered, however, it is not found persuasive. It should be noted that the enablement rejection is not based solely on the species specific immunostimulatory activities nor the variability of the immune response induced by oligonucleotides comprising the CpG motifs. The enablement rejection is made on the basis of the Wands factors. A conclusion of lack of enablement means that claimed subject matter was not described in the specification, in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the invention. In this case, the two cited points are directed at the lack of predictability present in the CpG art. The CpG art clearly notes that immunostimulatory activities vary from one species to the next. That is the immunostimulatory activities observed in mice would not necessarily be predictive of the immunostimulatory activities in humans. The CpG art also clearly cautions that the immune response in each oligonucleotide comprising the CpG motif is distinct from one another. That is, while Applicant has alleged that Applicant has disclosed a class of oligonucleotides that produces a Th1 biased immune response, however, as noted above, the Th1 associated cytokine profile induced by these oligonucleotides is distinct from one another. The existence of variability in the Th1 associated cytokine profile induced by each oligonucleotides comprising the CpG motif, depending on the length of the sequence, the sequences that flanks the CpG motif, the number of CpG motifs...etc., would not enable the skilled artisan to predictably and routinely pick any oligonucleotide comprising the CpG motif, as encompassed by the claims, to treat bacterial infection. Additionally, it is noted that Applicant has alleged that the Office'

conclusion that the absence of TLR9 in some species would lead to variability in results is misplace because Mutwiri et al. discloses that in vitro stimulation of cells by CpG motifs is conserved across species. It appears that Applicant has misconstrued the Office's conclusion. As noted in the previous office action:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[1] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice.[2] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.

The conclusion noted by the Office is the level of Th1 immune response is also dependent on TLR-9 expression, which varies from one species to the next. Moreover, the Office directs Applicant's attention to Krieg et al.[3] Krieg et al. clearly notes that because the cellular patterns of TLR expression varies between different species, the results of TLR stimulation in one species may not be predictive of what will occur in another. The disclosure of Krieg et al. clearly substantiates the Office's conclusion.

---

[1] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]
[2] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]
[3] Krieg et al. Antiinfective Applications of Toll-Like Receptor 9 Agonists. Proc. Am. Thorac. Soc., Vol. 4, 2007, 289-294.

Applicant also argues that Applicant has shown that the CpG oligonucleotides induce IFN-gamma, production of antibody responses, stimulation of B, NK and monocytic cells, and other cytokines. In view of this, Applicant argues that the data supports Applicant's assertion that the oligonucleotides are useful in treating bacterial infection. Applicant also argues that Applicant has provided sufficient direction and guidance in the specification. Applicant further argues that there is no evidence of unpredictability.

Applicant's assertion has been noted, however, it is not found persuasive. As noted by Applicant, all Applicant has discovered is the potential use of the oligonucleotides in treating bacterial infection. Applicant has fallen short of demonstrating that the oligonucleotides treat bacterial infection. Additionally, contrary to Applicant's assertion, Applicant has not provided sufficient direction and guidance in the specification. In the instant case, Applicant has disclosed of a single oligonucleotide that is therapeutic against bacterial infection. Applicant's assertion that unpredictability does not exist with the claimed invention has been noted. However, contrary to Applicant's assertion, the Office has clearly established that a high level of unpredictability does accompany the claimed invention. Furthermore, Applicant has not stated that the claimed invention is predictable.

Thus, while all of Applicant's arguments and criticisms have been carefully considered, the entire submission is not sufficient to overcome the enablement rejection. In this case, Applicant has fail to evidence that the claimed subject matter

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

As previously presented, in response to the rejection, Applicant argues that while the Office alleges that undue experimentation would be imparted upon the skilled artisan, the Office has never actually stated what the undue experimentation was that is required to practice the claimed invention.

This submission has been considered, however, contrary to Applicant's assertion, the Office has indicated the type of experiments that the skilled artisan would have to conduct in order to practice the claimed invention. In the instant case, the skilled artisan would have to unduly experiment with every aspect of the claimed invention. As stated in the enablement rejection, Applicant has not provided a nexus between the immunomodulatory activities of CpG oligonucleotides and bacterial infection. All Applicant has disclosed in the specification is that CpG oligonucleotides are immunomodulatory. From this discovery, Applicant asserts that these CpG oligonucleotides can be used to treat bacterial infection. The assertion is not substantiated by any evidence showing that the immunomodulatory activities accorded by these CpG oligonucleotides are therapeutically effective in treating bacterial infection. In the instant case, all Applicant has provided is an association study. This study does not commensurate with the claimed invention, a method of treating bacterial infection with the administration of a CpG oligonucleotide. In the instant case, Applicant's disclosure is merely an invitation to experiment. An invitation to experiment with immunomodulation, its effects on cytokines, and how it relates to bacterial infection.

The skilled artisan practicing the claimed invention would have to experiment with every parameter involved with the claimed invention, immunomodulation, cytokine production, and how all of it relates to bacterial infection. Applicant's disclosure is merely a suggestion to treat bacterial infection with the immunomodulation accorded by CpG oligonucleotides. Applicant has fallen short of demonstrating that CpG oligonucleotides are indeed therapeutically effective against bacterial infection. Furthermore, it should be noted that the enablement rejection is made if a determination of undue experimentation would be required of the skilled artisan practicing the claimed invention, in view of the Wands factors. Thus, for Applicant's future reference, the Office does not have to specify the type of undue experiments that the skilled artisan would have to perform to render the specification not enabling. It is the conclusion of undue experimentation, via the Wands factors, that is necessary to establish that the specification is not enabling for the claimed invention. The establishment of a nonenabling disclosure has thoroughly been provided to Applicant.

Applicant argues that, as taught in the specification, that CpG oligonucleotides should be administered to a subject to treat bacterial infection. Applicant then submits that the claimed invention was based on the discovery by Applicant that CpG oligonucleotides stimulated a potent immune response and that Applicant has asserted that such activity is predictive of bacterial infection.

This argument has been considered, however, it is not found persuasive. As Applicant has noted, Applicant asserted the predictive use of CpG oligonucleotides to treat bacterial infection. This is an assertion. Applicant has not supported Applicant's

assertion of predictability with any evidence that commensurate with the claimed invention, a method of treating bacterial infection with the administration of CpG oligonucleotides. Furthermore, as noted by Applicant, Applicant has discovered that CpG oligonucleotides stimulated a potent immune response. That is all Applicant has discovered. This discovery does not commensurate or equate to a method of treating bacterial infection. The gap between immunomodulating activity and treatment of bacterial infection using such activities is too big to bridge without undue experimentation. Applicant has not even defined the specific immunomodulatory activity necessary for treatment of bacterial infection. Nor has Applicant has disclosed whether the immunomodulatory activity is directed at an up or down regulation of this activity. In the instant case, the immune system is multifunctional and dynamic, and not as static as alleged by Applicant. In this case, one of ordinary skill in the immunology art would readily recognize the importance of immune modulation to treat a condition, however, all would also readily recognize that harnessing the necessary immune modulation is difficult to ascertain.

Applicant further argues that the issuance of the enablement rejection is made because the specification does not contain an in vivo working example.

This argument has been considered, however, contrary to Applicant's assertion, the enablement rejection is not solely based on the lack of working examples. In this case, it appears that Applicant has not fully grasped the enablement requirement. The rejection is made using the Wands factors as a whole.

Applicant argues that since the initial burden is on the Office to give reasons for the lack of enablement, the Office must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. In this case, Applicant asserts that a correlation between CpG oligonucleotides and their use in the treatment of bacterial infection.

Applicant's submission has been considered, however, it should be noted that Applicant has not conducted any in vitro or in vivo experiments that commensurate with the claimed invention. All Applicant has conducted are in vitro analysis of the immunomodulatory activity accorded by CpG oligonucleotides. Applicant has not even made the effort to characterize the in vitro efficacy of such oligonucleotides against bacterial infection. Thus, while the Office appreciates the immunomodulatory activities described in the specification, such is not sufficient to demonstrate as an in vitro analysis that shows a correlation between the use of CpG oligonucleotides and treatment of bacterial infection. At the very most, Applicant has provided an association study between CpG oligonucleotides, the immunomodulatory activities of such oligonucleotides, and the suggestion of use of the activities to treat bacterial infection.

Applicant further argues that the specification contains data that is sufficient to support Applicant's conclusion that the claimed compounds would be useful for treating bacterial infection.

This argument has been considered, however, as provided by Applicant, Applicant has only provided assertion that the compounds would be useful for treating bacterial infection. Applicant has not demonstrated that the compounds are indeed

useful in treating bacterial infection. Applicant has not taught the skilled artisan in the art how to use the claimed invention, administration of CpG oligonucleotides, to treat bacterial infection. All Applicant has provided are assertions of use based on the immunomodulatory activity of CpG oligonucleotides. Applicant has not even made an effort to characterize the type of immune modulation necessary to treat bacterial infection. Applicant is reminded that arguments and assertions cannot take the place of evidence where evidence is necessary. In the instant case, the evidence necessary to overcome this rejection is that the administration of a CpG oligonucleotide therapeutically treats bacterial infection or that the skilled artisan would be able to practice the claimed invention without undue experimentation. In this case, it is found that, in view of the Wands factors, the high level of unpredictability recognized in the art, the absence of working examples showing that CpG oligonucleotides treat bacterial infection, and any guidance or direction demonstrating that such oligonucleotides are therapeutically effective against bacterial infection, the skilled artisan would not be able to practice the claimed invention without the burden of undue experimentation.

Applicant further argues that the method need not be ready for clinical application in order to be enabled.

This submission has been considered, however, it should be noted that the method need to be disclosed in the specification in such way to enable the skill artisan to practice the claimed invention without undue experimentation. In this case, the enablement standard is not based on the presence or absence of clinical application or study. While a clinical application or study can be used as evidence showing the

enabling nature of the claimed invention, however, the absence of such application or study does not signify a lack of enablement. The absence of clinical application or study is not considered in evaluating the enabling nature of the claimed invention.

In response to the rejection, Applicant argues that the claimed invention is not directed at the administration of cytokines, yet, it is directed at the administration of CpG oligonucleotides to treat bacterial infection.

Applicant's submission has been considered, however, it should be noted that, as provided in the specification that the claimed invention is directed at the administration of CpG oligonucleotides to modulate an immune response including stimulating a Th1 patter of immune activation, cytokine production to treat bacterial infection. Thus, while the claimed invention is directed at the administration of cytokines, the claimed invention relies on the production of cytokines, as induced by a Th1 and/or Th2 stimulation to treat bacterial infection. In view of this, the Offices cited the cytokine art, which teaches that the use of cytokine to induce an immune modulation to treat a condition is unpredictable. Thus, while it may appear to Applicant that the Office has misconstrued what is being claimed by Applicant, it should be noted the Office fully grasps the invention being claimed. Furthermore, as stated in the previous office action, the enablement rejection is made on the basis of the Wands factors as a whole, and it is not limited to one or two of the factors. In this case, the citation of cytokine art demonstrates the unpredictability associated with the use of cytokine to treat a condition.

In addition to above, Applicant criticizes the Office interpretation of the disclosure of Auricchio et al. Applicant argues that contrary to the Office's position, the question of further characterization does not render the teachings of Auricchio et al. unpredictable.

This argument has been considered, however, it is not found persuasive. Auricchio et al. establishes that years after the filing of the instant patent application, further characterization of the mechanism by which CpG indirectly promotes the killing of *M. tuberculosis* is needed [Last sentence of paragraph bridging pages 917-918; and last sentence of first full paragraph on page 918.] In this case, Auricchio et al. establishes that much is unknown about CpG when Auricchio et al. discloses that further characterization of the mechanism is necessary. This disclosure is indeed a scientific question to determine if other mediators may playa role in MTB. In the instant case, it is readily apparent that the mechanism of action provided by CpG oligonucleotides is unknown. The absence of an understanding of the mechanism of action in which CpG played in MTB, further emphasize that the use of CpG to treat a condition is unpredictable. In the absence of an understanding of the mechanism in which CpG operates, the skilled artisan cannot predictability use CpG in the manner that it is desirable.

Applicant further take issue with the Office's reading of Klinman, Conover and Coban. Applicant assert that the finding noted by Klinman, Conover and Coban that there are "only a limited number of setting in which such a short term protection may be of therapeutic benefit" does not evidence that the claimed invention does not work.

Applicant's criticism has been noted, however, it appears that Applicant did not clearly comprehend the Office's reading of Klinman, Conover and Coban. As noted by Applicant, the teachings of Klinman, Conover and Coban does not evidence that the invention does not work. Had Klinman, Conover and Coban evidences that the invention does not work, a utility rejection would have also been proper. In the instant case, Klinman, Conover and Coban evidences the therapeutic benefit also depends on a limited number of settings. The presence of only a limited number of settings evidences that the skilled artisan practicing the claimed invention will have a difficult time doing so. Compounding with this and other noted difficulties that surround the nature of the claimed invention, it would be impossible for the skilled artisan to practice the claimed invention without an undue burden of experimentation.

Applicant further criticizes that the Office has misinterpreted the teachings of Raghavan et al. Applicant notes that Raghavan et al. teaches that CpG oligonucleotides provide a consistent reduction in bacterial load and is supportive of the predictability in the art, and the observation made by Raghavan et al. that CpGs have no direct antibacterial effect in vitro is irrelevant.

Again, Applicant's criticism has been noted, however, contrary to Applicant's assertion, the in vitro observation noted by Raghavan et al. speaks volumes to the magnitude of unpredictability noted for the nature of the claimed invention. In this case, Raghavan et al. evidences that in vitro data do not support or correlate with in vivo data. In the absence of a correlative between the two experimental settings, one skilled in the

art would have a difficult time practicing the claimed invention without an undue burden of experimentation.

Applicant also criticizes the Office's reading of Juffermans, who teaches that protective immunity varies among IFN-gamma gene proficient and deficient mice, and the Office's notation that the claims do not require the treatment population to be either IFN gamma proficient or deficient. Applicant further argues that it is unclear how the presence or absence of IFN-gamma reads on the predictability of the art and/or enablement of the claimed invention.

This submission has been considered, however, like many of the responses provided above, the presence or absence of IFN-gamma speaks volume to the unpredictability of the claimed invention. In instances where the resolution of bacterial infection is dependent on the immunomodulation that induces the production of interferon-gamma, provided by the CpG oligonucleotide, the skilled artisan would not be able to effectively treat subjects that are interferon-gamma deficient. In this case, Applicant has failed to provide any guidance relating to the type of immunomodulatory activity that is necessary to treat bacterial infection. In the absence of such guidance, all Applicant has done is suggest that the skilled artisan blindly experiment with each immunomodulatory and relates that to a CpG oligonucleotide and the treatment of bacterial infection. Additionally, while it is noted that the Juffermans et al., in his abstract, provides that CpG oligonucleotides given 2 weeks after infection were still able to reduce mycobacterial outgrowth. This teaching pertains to a reduction in

mycobacterial outgrowth. It does not commensurate with the therapeutic efficacy of CpG oligonucleotides against bacterial infection, as instantly claimed.

Regarding the teachings of Krieg et al., Applicant argues that a person of ordinary skill can rely on the routine art to find treatment regimen that are effective, thereby avoiding excessive immune activation.

This submission has been considered, however, while the definition of a treatment regiment is routinely practiced in the art and can readily be ascertained by one of skilled in the art, however, the issue relating to the claimed invention is not merely limited to defining the treatment regiment. In this case, the issue relates to the undue experimentation that the skilled artisan would have to conduct in order to arrive at the claimed invention. The skilled artisan must unduly perform these experimentation before he can pass it to one of ordinary skill in the art to refine or define a proper treatment protocol. In this case, the teachings of Krieg et al. demonstrate that even the determination of a treatment protocol is not as straightforward as one of ordinary skill in the art might expect. Krieg et al. clearly emphasis that the improper treatment protocol can lead to excessive immune activation. With this teaching in mind, the skilled artisan would not be motivated to blindly administer any CpG oligonucleotide, at any dose, as suggested by the claimed invention, to activate an unknown/undefined immune response that treats bacterial infection.

Applicant additionally also asserted that the Office has misconstrued the teachings of Hayashi et al., who teaches that CpG decreases intracellular growth of M. avium by 68%.

This submission has been considered, however, as it relates to the many other references that Applicant has been argumentative against, the teachings of Hayashi et al., a reduction in bacterial growth, is not equivalent to the treatment of bacterial infection. The reduction of bacterial growth does not speak to the therapeutic effect of CpG against a bacterial infection.

Applicant further notes that Applicant does not need to demonstrate that the invention is completely safe, while citing Klinman, Verthelyi, Takeshita and Ishii, who discloses that a balance of the safety concerns, toxicity has not been observed in normal animals injected with therapeutic doses of DNA vaccine or CpG oligonucleotide.

This submission has been considered, however, Applicant reminded that this is an enablement rejection. The standard of enablement is not whether has demonstrated that the invention is completely safe. This Office is not the Food and Drug Administration. In the instant case, the specification failed to evidence that the administration of CpG oligonucleotide treats bacterial infection. While it may be true that a balance of the safety concern can be achieve, however, it is one of the many concerns that the skilled artisan must further experiment in order to practice the claimed invention. In this case, Applicant has not demonstrated anything but an association between immunomodulatory activities and CpG oligonucleotides.

Moreover, Application took issue with the Office reading of Gursel et al., who teaches that the immunostimulatory activities are being harnessed therapeutically. Applicant asserts that the teachings of Gursel et al. do not reflect any unpredictability in the art.

This submission has been considered, however, contrary to Applicant's assertion, the teachings of Gursel et al. provides that years after the filing of the claimed invention, the art recognizes that the immunostimulatory activities of CpG oligonucleotides are still being harnessed. This exemplifies that it has not been harnessed in the years since the filling of the claimed invention, which is many years ago. In the instant case, eve if the teachings of Gursel et al. may pertain to modification f specific delivery methods resulting in an increase bioavailability, the teachings of Gursel et al. does hint at the difference in bioavailability among specific delivery methods and how the variations affect the therapeutic use of CpG.

Applicant additionally cited the teachings of Zimmerman et al., who Applicant argues to have showed that CpG protected susceptible mice from leishmania infection when administered several weeks after infection.

This submission has been considered, however, in the absence of the actual reference, the Office cannot evaluate the merits of the reference, as it relates to the claimed invention.

Applicant further submits that Elkins et al. provides an understanding of the bacterial determinants that stimulate either inflammatory or lymphocyte dependent immune responses.

This submission ahs been considered, however, the teachings of Elkins et al. speaks to the ability of CpG oligonucleotides to modulate infection by intracellular pathogens. The teachings of Elkins et al. do not speak to the therapeutic efficacy of said CpG oligonucleotides to treat bacterial infection. Furthermore, Elkins et al. further

establishes that CpG oligonucleotides do not protect all bacterial infections, as instantly claimed. While it is noted that Applicant has cited the teachings of Raghavan et al. and Gomis et al. to contradict Elkins et al. latter teachings, it should be noted that the variability in the findings among researches speaks loudly to the unpredictability of CpG art. Moreover, it should be noted that the claimed invention is not solely limited to one species of bacterium, rather the specification also lists:

Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps (e.g., *M. tuberculosis, M. avium, M. Intracellulare, M. kansaii, M gordonae*), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter erogenes, Klebsiella pneuomiae, Pasturella multicoda, Bacteroides sp., Fusobacterium nucleatum, Sreptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira*, and *Actinomeyces israelli* [Paragraph bridging pages 14-15 of the specification.]

as part of the genus of bacteria encompassed by the claimed invention.

Furthermore, Applicant is reminded that the specification is required to be enabling at the time the invention was filed. In the instant case, none of the references

cited by Applicant to rebut the Office's position of unpredictability and undue experimentation required of the skilled artisan practicing the art establishes that the claimed invention is enabling at the time the invention was filed.

Lastly, Applicant strongly criticizes the Office for not addressing each point of Applicant's rebuttal to the art cited by the Office.

This criticism has been noted, and it should be noted that for every point made by the Office, Applicant argues that the point is not relevant for one reason or another. However, as established above, every point made by the Office in the rejection is of relevance. These points speak to the difficulties, trials and unpredictability that the skilled artisan would have to endure trying to practice the claimed invention. With the high degree of difficulties and unpredictability, the skilled artisan would not be able to practice the claimed invention without an undue burden of experimentation. In the instant case, while the Office clearly recognizes Applicant's point that the claimed invention is not directed at the administration of cytokines, rather the administration of CpG oligonucleotides to treat bacterial infection. However, Applicant cannot deny that the activities in which the claimed invention relies on to render treatment for bacterial infection is the immunomodulatory activities of the CpG oligonucleotides. And Applicant's disclosure clearly suggests the use of this immunomodulation, which includes the induction of a Th1 immune response and the production of Th1 associated cytokines. Thus, in view of the nature of the claimed inventing, the Office cited teachings in the CpG art, cytokine art, and Th1 immune response art to demonstrate the

difficulties and unpredictability that is awaiting the skilled artisan attempting to practice the claimed invention.

Additionally, Applicant argues that Applicant has provided sufficient direction and guidance in the specification.

This argument has been considered, however, the opposite is true. Contrary to Applicant's argument and belief, the specification does not contain any guidance or direction pertaining to the therapeutic efficacy of CpG oligonucleotides to treat bacterial infection. All Applicant has provided in the specification is an association between the immunomodulatory activities accorded by CpG oligonucleotides and the suggestion of taking advantage of the activities to treat bacterial infection. Applicant has not even characterized the activities to render a conclusion on the effectiveness of such activities on bacterial infection.

Regarding the predictability or unpredictability in the art, Applicant asserted that the Office has failed to evidence that the practice of the claimed invention is unpredictable.

Applicant's arguments have been considered, however, it is not found persuasive. In the instant case, the Office has fulfilled its burden in establishing a prima facie case of a lack of enablement. The Office's position is further exemplified by the art cited by Applicant to prove that the claimed invention is predictable. As noted above, Raghavan et al. demonstrates that in vivo and in vitro data do not correlate with one another, Elkins et al. establishes that not all bacterial infection are equally

immunoprotective by CpG oligonucleotide, and Gursel et al. teaches that the immunostimulatory activities are being harnessed therapeutically.

It is noted that Applicant asserted that Applicant has enclosed copies of several references demonstrating the positive effect of CpG oligonucleotides in the treatment of bacterial infection, listed on an IDS.

This assertion has been noted, however, contrary to Applicant's assertion, no such document is found with Applicant's recent submission.

Applicant is reminded that to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not

have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

The broadest claim is directed to a process for treating bacterial infection in subjects with the administration of an oligonucleotide containing the CpG motif, wherein the oligonucleotide is stabilized.

Nature of the invention:

The nature of the claimed invention is directed at treating bacterial infections with the administration of an oligonucleotide that comprises the CpG motif in vertebrates diagnosed with said infection

Breadth of the claims:

The specification defines "subject" as a human or vertebrate animal including dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat and mouse. [Lines 27-28 of page 19 of the specification.] It should be noted that the specification is not limited humans, dogs, cats, horses, cows, pigs, sheeps, goats, chickens, rats and mice.

The specification also lists examples of infectious bacteria, which includes *Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps* (e.g., *M. tuberculosis, M. avium, M. Intracellulare, M. kansaii, M gordonae*), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Streptococcus*

pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter erogenes, Klebsiella pneuomiae, Pasturella multicoda, Bacteroides sp., Fusobacterium nucleatum, Sreptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira, and *Actinomeyces israelli*. [Paragraph bridging pages 14-15 of the specification.] It should be noted that the specification is not limiting "bacteria" to only those listed at the cited passage.

Thus, in view of the disclosure, the breadth of the claims encompasses:

- **all vertebrate animals**
- **all bacterium**
- **all nucleic acid sequences that contains the CpG motif.**

Thus, the broadest breadth of the claimed invention encompasses the use of any nucleic acid sequences containing the CpG motif to treat infections caused by all bacteria in all vertebrate animals.

State of the Art:

The art acknowledges the importance of Th1 type immune response, which stimulates the production of Th1 associated cytokines, in contributing to the elimination of intracellular pathogens such as mycobacterium and virus. However, the art also teaches that:

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, **host response to exogenously administered**

cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state.

- **Both Th1 and Th2 type of immune responses in necessary.** Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, **a tight control over where and when Th1 and Th2 immune responses happen is necessary**.[4]
- The **efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial.** For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection.[5]
- **Interleukin-12**, Th1 associated cytokine, induces different effector mechanisms that result in **either protection or exacerbation**.[6] Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice.

---

[4] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[5] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[6] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]

- **Interleukin 18,** a Th1 associated cytokine, is **responsible for the progression** of endotoxin-induced liver injury in mice primed with interleukin 18. [7]
- **Interleukin 6 and interferon gamma**, both are Th1 associated cytokines, **augment the susceptibility** of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utlitising **HIV-1** strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1.[8]
- **Interleukin 2**, a Th1 associated cytokine, **increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies.** Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. [9]
- **Interferon gamma is ineffective against the virulent strain of Mycobacterium avium.** Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma.[10]

In all, the art amply recognizes the following **limitations**: **inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects**.

---

[7] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[8] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]
[9] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

The art notes that the efficacy of exogenous cytokines capable of potentiating normal host defense mechanisms may be curtailed in immunocompromised patients lacking the pertinent effector cells or containing disease-related factors preventing lymphocyte activation. The art also notes that viral, bacterial and parasite adaptations to the presence of cytokines pose new problems and approaches based on cytokine intervention will have to take these factors into account.[11]

The CpG art teaches:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[12] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice.[13] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.
- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation

---

[10] Silva et al. Evaluation of IL-12 in immunotherapy and vaccine design in experimental Mycobacterium avium infections. The Journal of Immunology, 1998, Vo. 161, 5578-5585. [Last sentence, left column of page 5583, in particular.]
[11] Masihi, K., paragraph bridging left and right columns of page 646, in particular.
[12] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]
[13] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]

induced by these oligonucleotides varies.[14] The art frequently notes that the **specific nucleic acids**, purines and pyrimidines, surrounding the CpG motif, **influence both the level and type of immune stimulation**; the **spacings** between CpG motifs surrounding the CpG motif **influence both the level and type of immune stimulation;** and **t**he **type of cytokine stimulated** by oligonucleotides containing the CpG motif **varies from one oligonucleotide to the next**.[15, 16,17] The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence.[18]

- **In vitro observations do not accurately predict what happens in vivo**.[19]
- The **immunostimulatory activity of CpG oligonucleotides is species specific**. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.[20]

---

[14] Krieg et al., paragraph that bridge pages 716-717, in particular.
[15] Mutwiri et al., last sentence of paragraph bridging pages 89-90.
[16] Ibid.
[17] Ibid, third to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[18] Krieg et al., paragraph that bridge pages 712-713, in particular.
[19] Mutwiri et al., second to last sentence in the paragraph bridging left and right columns of page 90, in particular.
[20] Ibid, section 2.1, disclosed on page 90, in particular.

- The **immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another**.[21]

Presence or absence of working examples:

The specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection.

All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif. For example, the working examples note that the immunostimulatory effect and the extent of the immunostimulatory effect induced by oligonucleotides containing the CpG motif varies with the length of the oligonucleotide containing CpG motif; the number of CpG motifs present in the oligonucleotide; the nucleic acid(s) that flanks the CpG motif; the presence or absence of a modified phosphate backbone; and the presence or absence of methylated cytosine…etc.

Additionally, the working examples set forth that the immunostimulatory effect of oligonucleotides containing the CpG motif varies from one oligonucleotide to the next.

In addition, the working examples also demonstrate that an oligonucleotide having the sequence set forth in SEQ ID NO: 10, which contains the CpG motif is capable of stimulating the production of interleukin-12 and interferon-gamma, both of which are Th-1 associated cytokines. The working examples also demonstrate that oligonucleotides having the sequence set forth in SEQ ID NOs: 115, 19, 15, 116 and 18,

[21] Ibid, Table 1 on page 92, and first sentence in first full paragraph, left column of page 94, in particular.

all of which contains the CpG motif are capable of stimulating the production of interleukin-6, a Th-1 associated cytokine in vitro; and oligonucleotides having the sequence set forth in SEQ ID NOs: 124 and 16, which also contain the CpG motif, are not capable of inducing interleukin-6 to the extent that is higher than the control, media. Additionally, the working example shows that an oligonucleotide having the sequence set forth in SEQ ID NO: 48, which also contains the CpG motif and a modified phosphate backbone are capable of inducing interleukin-6 production in vivo.

Lastly, the working examples demonstrates that oligonucleotides having the sequence set forth in SEQ ID NOs: 28-29, 101, 104-105, 7 and 3, all of which contains the CpG motif are capable of stimulating the production of interleukin-6, tumor necrosis factor-alpha, interferon-gamma, GM-CSF, and interleukin 12, Th-1 associated cytokines in human PMBC. And oligonucleotide having the sequence set forth in SEQ ID NO: 102, which contains a CpG motif, is capable of inducing just interleukin-6, tumor necrosis factor-alpha, GM-CSF, and interleukin 12. The oligonucleotide having the sequence set forth in SEQ ID NO: 102 does not induce interferon-gamma production. Furthermore, the oligonucleotide having the sequence set forth in SEQ ID NO: 103, which contains a CpG motif, is capable of inducing just interleukin-6, interferon-gamma, tumor necrosis factor-alpha, and GM-CSF. The oligonucleotide having the sequence set forth in SEQ ID NO: 103 does not induce production of interleukin-12.

Amount of direction or guidance presented:

Beside a discussion of how various structural modification effects the immunostimulatory activity of oligonucleotides, as exemplified by the working

examples, Applicant has not provided any direction or guidance directed at the use of any of the disclosed oligonucleotides containing CpG motif to treat bacterial infections in vertebrate.

All that is gathered from the specification is the contemplation of apply the generic immunostimulatory activity that is sometimes observed with oligonucleotides containing the CpG motif, to treat, prevent, or ameliorate bacterial infection. [Lines 5-15 of page 9.] It is also noted that the specification prefers nucleic acid sequences that stimulate cytokine production, particularly IL-l, IL-12, IFN-gamma, TNF-alpha, and GM-CSF. [Lines 24-30 of page 8.]

Predictability or unpredictability of the art:

As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable. The level of immune stimulation varies from one oligonucleotide to the next. The type of cytokine stimulated by oligonucleotides containing CpG motif also varies from one oligonucleotide to the next.

In addition, as demonstrated by the cytokine art, the use of cytokines in the treatment of diseases is unpredictable. The art notes that the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines contribute to the spontaneity that is observed in treatment of infections with the cytokines.

Quantity of experimentation necessary:

In the instant, Applicant has not provided a nexus between the activities observed for various oligonucleotides containing the CpG motif and bacterial infections.

Applicant has not provided any guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections. Applicant has provided any guidance pertaining to the type of activity that would need to be stimulated to provide effective treatment against bacterial infections. Applicant has not provided any guidance relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections. In all, Applicant has failed to provide any guidance relating the treatment of bacterial infection with oligonucleotides containing CpG motif.

In view of the complete absence of any guidance relating the claimed invention and the different immunostimulatory activities that is observed in the specification, the skilled artisan cannot possible practice the claimed invention without extreme research and experimentations. **To practice the claimed invention, the skilled artisan would have to conduct extensive research and experimentation**.

Thus, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat bacterial infections; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan cannot possibly practice the claimed invention without an undue burden of research and experimentation.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent

the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. The double patenting rejections over 10/735592, 10/894862 and 10/224523 are witdrawn in view of Applicant's submission. In response to the double patenting rejections over 10/613916 and 10/787737, Applicant defers rebuttal until the claims

are allowed, which has been noted. Until the rejections are properly addressed, the rejections are maintained in the record.

9. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/613916.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 19 of the conflicting patent application is directed at the treatment of mycobacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C.

The difference between the two claims is that claim 19 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the generic recitation CpG.

The other difference between the two claims is that the conflicting patent application does not require the oligonucleotide to be stabilized. However, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to have stabilized the oligonucleotide by modifying the phosphate backbone. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to increase the half-life of the oligonucleotide. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of

success for doing so because stabilization of nucleic acid sequences is well known in the art.

The last difference between the two claims is that claim 19 of the conflicting patent application recites mycobacterial infections instead of bacterial infections. However, it is noted that mycobacterial infections is encompassed by the generic bacterial infections.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claim 104 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 10/787737.

Claim 104 of the instant patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject; wherein the oligonucleotide is a stabilized oligonucleotide.

Claim 38 of the conflicting patent application is directed at the treatment of bacterial infection in a subject with the administration of an oligonucleotide comprising the CpG to said subject, wherein the CpG motif comprises an unmethylated C, and wherein the oligonucleotide is a stabilized oligonucleotide.

The difference between the two claims is that claim 38 limits the C residue in the CpG motif to unmethylated C. However, unmethylated C is a cytosine, which is encompassed by the recitation CpG.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. A terminal disclaimer to U.S. Patent No. 6207646 is noted of record.

Conclusion

12. No claims are allowed.

13. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Le/
Patent Examiner, Art Unit 1648

/E. L./